Fungicides and Fumigants

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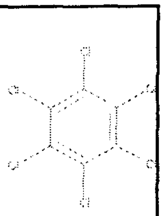
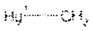
Presentation Overview

- Fungicides and Fumigants, 2002
  - Emphasis on active ingredients with current registrations in U.S.
    - Regulatory transitions for certain substances
  - Modern epidemiology of human exposures
    - Occupational and non-occupational
  - Relevant chemistry
    - Environmental fate
  - Clinical toxicology
    - Toxicokinetics
    - Toxicodynamics
    - Biomarkers of exposure
    - Therapeutic options
  - Aspects of prevention

Fungicides



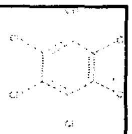
Hexachlorobenzene



Methylmercury

- Historical importance
  - Hexachlorobenzene (HCB)-Turkey, 1955
    - Consumption of wheat
      - Seed treated with 10% HCB
    - Porphyria cutanea tarda
    - 5,000 cases
  - Methylmercury-Iraq, 1971
    - Chronic ingestion of wheat
      - Wheat had been treated with MeHg as fungicide
    - Target organ effects on neurological system
    - 50,000 exposures, 439 fatalities
- Epidemiology of Modern Fungicides
  - Low prevalence of exposures, relative to other pesticides
    - <2% of pesticide exposures in U.S. (TESS, 2001)
    - Lower case morbidity, mortality rate than other pesticide classes

Pentachlorophenol



PCP

- Chlorinated derivative of phenol
  - Broad pesticidal properties
- Designated restricted use pesticide (RUP) in 1984
  - Most uses as herbicide, antimicrobial, were discontinued
  - Current uses in wood treatment
    - Not for log homes or building interiors
  - Current uses as antimicrobial (biocide)
    - Oil field flood waters
    - Pulp and paper mill solutions
- Labeling allows sale and use only to certified applicators
  - Prohibits application to logs for log homes

Pentachlorophenol: Reports of Occupational Exposures

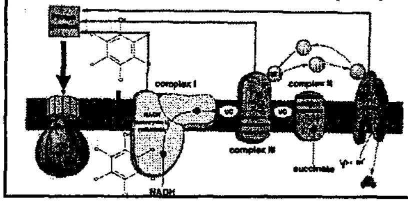
- Acute effects reported from several exposure scenarios
  - Inhalation exposure when *dipping* wood in liquid
  - Immersion of hands in PCP solutions
  - Brushing PCP onto logs for log cabin construction
- Chronic effects have been reported
  - Epidemiological associations with cancer
    - NHL, multiple myeloma, soft-tissue sarcomas
      - Classified B2 (Probable) by EPA
        - Sufficient data in animals
        - Inadequate data in humans
      - Possible human carcinogen (IARC)
  - Toxicological mechanisms unclear

PCP

PCP Toxicokinetics and Toxicodynamics (Acute Exposure)

- Toxicokinetics:
- Well-absorbed by inhalation and dermal pathways
- Wide volume of distribution
- Parent compound responsible for toxic effects

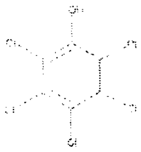
- A weak, lipophilic acid
- Crosses the inner mitochondrial membrane
- Disrupts normal production of ATP by bypassing ATP synthase complex
- **Uncoupling oxidative phosphorylation**

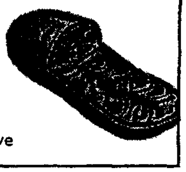


Mitochondrion

Pentachlorophenol Toxicology: Clinical Effects

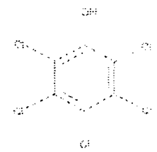
- Uncoupling of oxidative phosphorylation
  - generates heat
  - inability to form ATP from aerobic metabolism
    - *Shift to anaerobic metabolism*
- Results in hyperthermia
  - Core temp > 106 F reported in severe cases
  - Refractory to cooling measures
    - Rapid onset of neurological symptoms, *delirium*
    - Tachycardia, tachypnea
    - *Rhabdomyolysis*
    - Lactic acidosis
    - Immediate onset of extreme rigor mortis
- No antidotes
  - Importance of dermal decontamination
  - Rapid cooling
  - Many cases do not survive despite aggressive supportive management

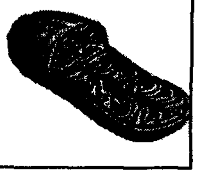




Pentachlorophenol Toxicology: Biomarkers of Exposure

- Parent compound detectable in blood, urine
  - Most excreted as PCP, some as glucuronide conjugate
- Interpretation of levels difficult
  - Detectable in general population
    - Levels ~ ppb-ppm range
  - Acute toxicity associated with levels ~100ppm
  - Limited prognostic value for occupational exposure surveillance



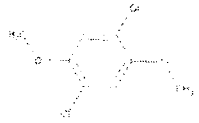


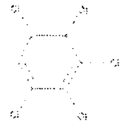
Preventing Unnecessary Exposure: Pentachlorophenol

- Restricted use pesticide
  - Education, training
  - Compliance with labeling instructions
  - Recognizing workers at risk of exposure
- Occupational exposure limits
  - OSHA PEL: 0.5 milligrams of pentachlorophenol per cubic meter of workplace air (0.5 mg/m^3) for 8 hour shifts and 40 hour work weeks
    - Same as NIOSH REL

Other Substituted Benzene Fungicides

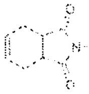
- Potential irritants, dermal sensitizers
  - No reports of systemic toxicity
- Chloroneb
  - Formulated as wettable powder
    - Treatment of soil, seed
  - Moderate skin irritant (animals)
- Pentachloronitrobenzene
  - Soil fungicide, seed treatment
  - Case reports of dermal sensitization
  - No reports of methemoglobinemia from occupational exposure

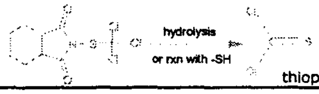

chloroneb


pentachloronitrobenzene (PCNB)

Pthalimido (Chloralkylthio) Fungicides

- Captan
  - Reports of dermal sensitization (humans)
    - Severe eye irritant in animal studies
  - No reports of toxicity from systemic absorption
- Low rate of dermal absorption
- Rapid metabolism and elimination
  - Biomarkers for major metabolites have been developed
    - Not currently used clinically, or for surveillance
- Hydrolysis of pthalimido compounds yield thiophosgene
  - Highly reactive intermediate

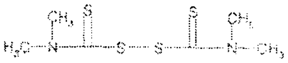

captan

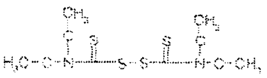


thiophosgene

Dialkylthiocarbamates

- Widely used fungicides
- Chemistry: effects differ from N-methyl carbamates (aldicarb, as example)
  - Not cholinesterase inhibitors
- Thiram
  - Component of latex
  - Sensitization reactions
- Structural similarity to disulfiram (Antabuse)
  - Inhibit acetaldehyde dehydrogenase
    - Antabuse reactions
  - Antabuse reactions in workers exposed to thiram?
    - Not reported in context of fungicide use

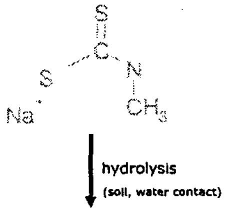

thiram


disulfiram

Dithiocarbamates: Metam-Sodium

- A dithiocarbamic acid
- Registered applications as general and RUP
- Broad spectrum soil fumigant
- Stable at pH 8
- Hydrolytic decomposition products are volatile
    - Methyl isothiocyanate
        - Major product
    - Hydrogen sulfide
    - Carbon disulfide

Metam-Sodium

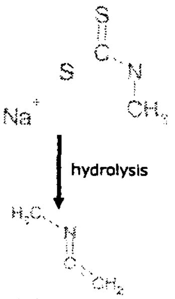


MITC

Metam-Sodium

- Technical grade Metam-sodium
    - Moderate to severe irritant
    - *Skin sensitizer*
- Methylisothiocyanate (MITC)
    - *reacts strongly* with sulfhydryl groups (cellular proteins)
        - tissue injury
        - *Not cyanogenic*
    - Odor threshold ~100-500 ppb
    - *Threshold* for irritant effects < odor threshold (no warning properties)
- Human epidemiology (Cone JE, et al., Chest 1994;106:*500*-8)
    - 1991, train derailment
    - *19,000 gallon spill*
        - Sacramento River
    - Massive kill of aquatic organisms
    - Dermatitis, asthma exacerbation, persistent irritant-induced RADS

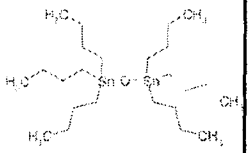
Metam-sodium



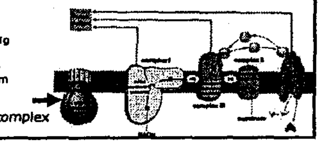
Methyl isothiocyanate

Organotin Fungicides

- TBTO uses in marine paints (*antifoulant*)
    - Concerns about environmental impact, marine organisms and wildlife
    - Human exposure from dietary pathways
- Reports of *adverse* effects from indoor use (paint additive, carpet fungicide)
    - Irritant effects *on airways*, mucous membranes
    - Contact dermatitis
- Animal toxicology studies
    - Potent eye, skin irritants
    - Immuno*toxic* effects
        - Thymic atrophy, *diminished Ig* responses
    - *Endocrine* modulatory effects
        - Reduced testicular size, sperm production
    - *Mechanism*: inhibitors of mitochondrial ATP synthase *complex*

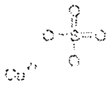


tributyltin oxide (TBTO)

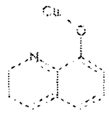


Copper-Containing Fungicides

- Common cause of morbidity, mortality from accidental, intentional ingestion outside U.S.
    - Corrosive injury to GI tract
    - Centrilobular necrosis in liver
    - Oxidative stress
        - Heinz body formation in Hb
        - Methemoglobinemia
- Occupational exposures
    - irritating to skin, mucous membranes
    - Limited bioavailability from dermal pathways
    - No reports of systemic toxicity
- Biomarkers of exposure to copper
    - Whole blood better than serum (acutely)
    - Not used for occupational surveillance of workers with Cu-fungicide exposure



Copper sulfate

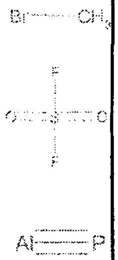


Copper quinolate

Fungicides Summary

- Diverse chemical structures, mechanisms of toxicity
  - Potential for irritant, sensitization effects from contact exposure
    - Substituted benzenes, pthalimido fungicides, dialkylthiocarbamates
  - Systemic toxicity
    - Pentachlorophenol, organotin compounds
- Limited role of biomarkers in exposure surveillance
- Importance of recognizing workers at risk
  - Education and training

Fumigants

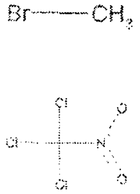


- Diverse chemical structures
- Utilized to control pests in enclosed spaces, soil, and structures
- Modern epidemiological data suggest fewer exposure cases than fungicides
  - TESS, 2001
    - 674 cases of over 90,000 pesticide exposures
    - Majority of cases (65%) in association with sulfuryl fluoride
- Higher case-severity and case-fatality rate than fungicides
  - Many exposures are accidental
    - Applicators, workers, non-occupational (residential)

Methyl Bromide (MeBr)

- Colorless, odorless gas
  - Heavier than air
    - Important in enclosed spaces
- Broad spectrum of activity
- Three main applications
  - Soil fumigation (pre-plant)
    - Direct injection to soil
    - Peppers, strawberries, tomatoes
  - Post-harvest commodity treatment
    - Eradicating pest infestations
    - Occurs in storage areas
  - Structural pest control
    - Termite control (enclosed structures)

Exposure to Methyl Bromide



chloropicrin

- Scenarios associated with accidental, occupational exposures
  - Inadequate ventilation of a treated structure
    - Applicators at highest risk
      - Critical importance of education, safety training, adherence to protective measures
      - Chloropicrin (*lacrimator*) added as warning agent
        - Irritation threshold ~ 1 ppm
    - Others at risk from early re-entry
  - Unanticipated cross-ventilation from a treated structure

Case Report: Accidental MeBr Exposure Leading to Fatality

©Chad Slattery, 1996

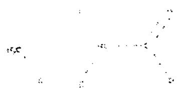
- Horowitz BZ, et al. (1998)
- Structural fumigation of a residence
  - Home appropriately tented, sealed
- Owner, fumigator unaware of 8 open pipes (1-2 inches in diameter) connecting residence to guest house
  - 2x2 foot trap door was covering pipes

$Br—CH_3$

Case Report: Accidental MeBr Exposure Leading to Fatality

- Adult female was occupying the guest house
- Developed headache, flu-like symptoms
- Within 24 hours, found in status epilepticus
- Initial labs remarkable for elevated CK, BUN, Cr, liver aminotransferases
- Subsequent course of fever (no source identified) rhabdomyolysis, persistent vegetative state
- Expired day 19 post-exposure
  - Detectable levels of MeBr in blood, bile, liver, and adipose tissue
  - MeBr detectable at 15 ppm in conduits 5 days post-fumigation
    - ACGIH TLV 1 ppm, OSHA PEL 20 ppm

Methyl Bromide Toxicokinetics


S-methylcysteine

- Highly lipid soluble
  - Well-absorbed via lungs, GI tract
- Wide volume of distribution
  - CNS
- Metabolism of MeBr occurs rapidly
  - MeBr has strong alkylating properties
    - Can carry out methylation reactions
    - Methylation of glutathione yields S-methylcysteine adducts
      - A potential biomarker of *exposure* to MeBr?
  - Some MeBr undergoes Phase II metabolism
    - Conjugation with glutathione
- Bromide ion undergoes urinary elimination
  - Elimination $t_{1/2}$ ~ *12 days* of Br^-
    - Some correlation with serum levels and degree of occupational exposure
- Parent compound (MeBr) *not* usually detectable in tissues

Methyl Bromide Toxicodynamics

- Toxicodynamics incompletely understood
  - Cell membrane disruption (result of high lipid solubility)
  - Altering critical enzyme function by alkylating sulfhydryl groups, DNA (mutagenesis)
    - *in vitro, in vivo* (animal) evidence
  - Role of individual genetic susceptibility?
    - Glutathione S-transferase expression?
- Target organ effects
  - Neurological system
  - Liver
  - Kidneys

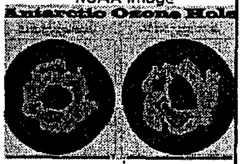
Methyl Bromide Toxicology: Clinical Effects

- Non-specific at lower acute levels of exposure
  - Mucosal irritation
  - Headache, dizziness
  - Nausea, vomiting
- Rapid onset of progressive symptoms with acute high levels of exposure
  - CNS depression, seizures, pulmonary edema
  - Skin injury, blistering reported with high-level dermal exposure
- Chronic exposure and neurological effects
  - Peripheral sensorimotor neuropathy
  - Central pyramidal, cerebellar dysfunction
- Sxs reversible with mild intoxication
  - Permanent effects have been reported in severe cases
- Management is supportive
  - No antidotes

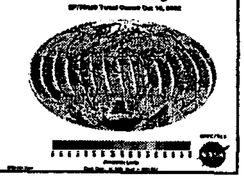
The Future of Methyl Bromide

- MeBr contributes to stratospheric ozone depletion
- U.S. and other countries in process of phasing out production and use
- Phase-out schedule
  - 25% reduction in 1999
  - 50% reduction in 2001
  - 70% reduction in 2003
  - 100% reduction in 2005
  - Critical and emergency uses allocated after 2005

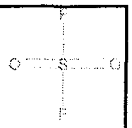
NOAA image



NASA image

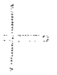


Sulfuryl Fluoride



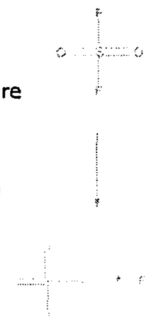
- Fumigant insecticide (Vikane)
  - First registered in 1959
  - EPA Re-registration review in 1993
    - Restricted use pesticide due to inhalation toxicity
- Sites of application differ from MeBr
  - Not registered for use on food or feed
  - Used in fumigation of closed structures and their contents
    - Domestic dwellings, warehouses, railroad cars
      - Termites, wood-destroying insects, rodents
  - Has been used to fumigate more than 1,000,000 structures since 1961
  - Does not contribute to ozone depletion

Sulfuryl Fluoride: Chemistry and Structural Application



- Colorless, odorless, non-flammable gas
  - Dispensed into an enclosed structure
  - Chloropicrin applied prior to sulfuryl fluoride
- Structure remains closed (no re-entry)
- Aeration of structure occurs prior to re-entry
  - 6-8 hour waiting period
- Highest risk of exposure is at time of application, and re-entry period
  - NIOSH-approved SCBA must be worn by applicators at time of re-entry
  - Portable analytical methods used by applicators to confirm concentration of sulfuryl fluoride < 5 ppm for re-entry
    - TLV (ACGIH, NIOSH), OHSA PEL = 5 ppm

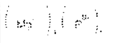
Sulfuryl Fluoride Toxicology



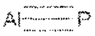
- Toxicokinetics not fully understood
  - Systemic absorption can occur with high-level inhalation exposure
    - Inhalation 2-hour LC_{50} (animal studies) 4,500 ppm
  - Metabolism yields fluoride ion
    - Elevation of serum fluoride has been reported in human poisonings
- Toxicodynamics unclear
  - Systemic effects of fluoride ion?
    - Hypocalcemia, hypomagnesemia, hypokalemia

Sulfuryl Fluoride and Human Toxicology

- Nervous system, lungs, heart as target organs of effect
  - Rapid onset, progression of symptoms
    - MMWR, September 18, 1987 / 36(36);602-4,609-11
    - Chest pain, dyspnea, disorientation, cardiac arrest
- Some cases with elevation of serum fluoride
  - Levels can be difficult to interpret
- No specific therapies have been identified
  - Supportive management
- Role for intravenous calcium in acute poisoning?
  - Questionable benefit on survival in experimental animal models
    - Could be of theoretical benefit in acute poisoning
    - Has not been investigated in humans



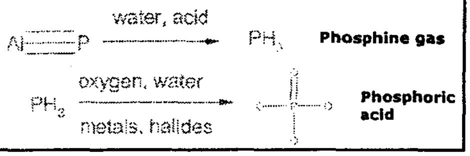
Phosphide Fumigants

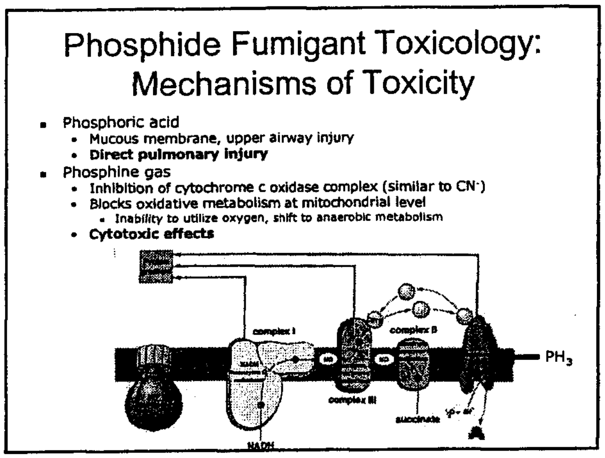


- Accidental and intentional exposures, occupational and non-occupational
  - Aluminum phosphide (AlP)
    - Registered for commodity fumigation and as rodenticide (RUP)
    - Some formulations contain ammonium carbonate
      - Releases ammonia and CO_2
      - Lowers potential for oxidation, combustion of AlP
  - Magnesium phosphide
    - Registered for commodity fumigation and rodenticide (RUP)
  - Zinc phosphide
    - Registered as rodenticide, some commodity uses
      - *GUP and RUP*
    - Higher degree of chemical stability than AlP
- Formulations include tablets, pellets, dusts, baits

Phosphide Fumigant Chemistry

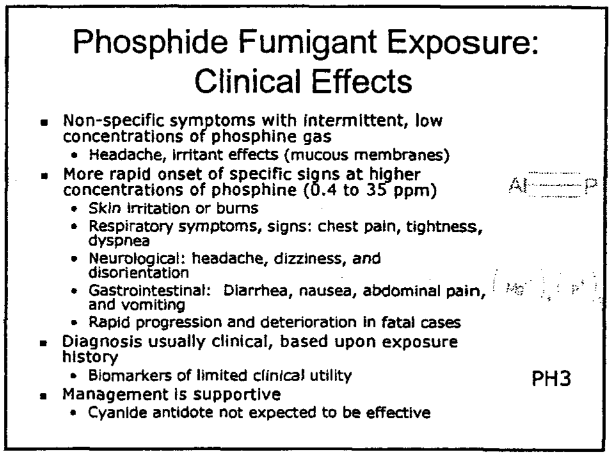
- Phosphides break down to phosphine gas
- Phosphine is the active fumigant
  - Colorless gas
  - odor threshold ~ 2 ppm
    - **Not a reliable indicator of occupational exposure**
      - NIOSH REL .3 ppm
- Phosphine can decompose to more stable forms (phosphoric acid)
  - At high concentrations of phosphine, an exothermic reaction
    - Can result in explosions





Phosphide Fumigant Toxicology: Mechanisms of Toxicity

- Phosphoric acid
  - Mucous membrane, upper airway injury
  - **Direct pulmonary injury**
- Phosphine gas
  - Inhibition of cytochrome c oxidase complex (similar to CN$^-$)
  - Blocks oxidative metabolism at mitochondrial level
    - Inability to utilize oxygen, shift to anaerobic metabolism
  - **Cytotoxic effects**

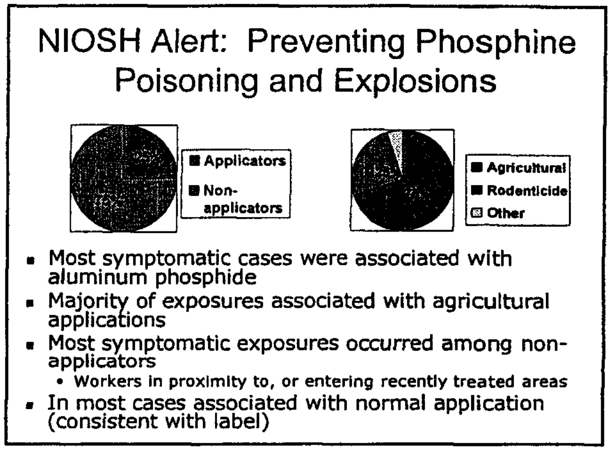


Phosphide Fumigant Exposure: Clinical Effects

- Non-specific symptoms with intermittent, low concentrations of phosphine gas
  - Headache, irritant effects (mucous membranes)
- More rapid onset of specific signs at higher concentrations of phosphine (0.4 to 35 ppm)
  - Skin irritation or burns
  - Respiratory symptoms, signs: chest pain, tightness, dyspnea
  - Neurological: headache, dizziness, and disorientation
  - Gastrointestinal: Diarrhea, nausea, abdominal pain, and vomiting
  - Rapid progression and deterioration in fatal cases
- Diagnosis usually clinical, based upon exposure history
  - Biomarkers of limited clinical utility
- Management is supportive
  - Cyanide antidote not expected to be effective

NIOSH Alert: Preventing Phosphine Poisoning and Explosions

- http://www.cdc.gov/niosh/99-126.html
- A review of 205 occupational exposure cases
- Common accidental exposure scenarios
  - Lack of proper handling during fumigant application
  - Failure to monitor air concentrations during application
  - Failure to use appropriate respiratory equipment
  - Improper disposal of unused fumigant products
  - Incidental exposure from nearby fumigant application



NIOSH Alert: Preventing Phosphine Poisoning and Explosions

- Most symptomatic cases were associated with aluminum phosphide
- Majority of exposures associated with agricultural applications
- Most symptomatic exposures occurred among non-applicators
  - Workers in proximity to, or entering recently treated areas
- In most cases associated with normal application (consistent with label)

Case Report from the National Pesticide Medical Monitoring Program

- Alabama, 2002
- Adult male, received container of 500 pellets aluminum phosphide
  - Pellets were stored in warehouse
  - Individual not trained in its use
- Applied pellets to ground floor of his home residence to control rodents
  - Two occassions
    - Second occasion followed by high rainfall, humidity
- Adult male and grandmother found dead next morning after second application
  - Other environmental causes ruled out

2001: EPA Memorandum of Understanding (AIP Fumigants)

- Issued subsequent to EPA RED (1998)
- Agency concerns
  - Risk mitigation for applicators, bystanders
- Provisions of Agreement
  - Fumigation management plans for users of phosphide fumigants
    - Site suitability, notification measures, emergency procedures
  - Monitoring studies
    - Rate of dissipation at varying distances from application site
  - Re-evaluation of current safety limits for phosphine
    - May be lowered
  - Strengthen training and certification process
  - 2-year incident reporting requirements of manufacturers (registrants)
    - 6(a)2 process (through FIFRA)

Fumigants, 2002: Summary

- A time of transition
  - Phase-out of methyl bromide
    - ? Increase in sulfuryl fluoride, phosphide fumigants, other alternatives
- Can pose acute risks from inhalation pathways
  - Occupational: applicators and non-applicators
  - Non-occupational: accidental and intentional
- Diverse chemical properties, mechanisms of toxicity
  - Limited, if any, role of biomonitoring at this time
  - Limited therapeutic options
- Need for improved recognition, reporting adverse incidents by OEM providers
  - Emphasis on preventive interventions

Fungicides and Fumigants

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